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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/899,807	Honda
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above, claim(s) *6-11, 13, 19-24, 26, 41-44, 46, and 48-52* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 12, 14-18, 25, 27-40, 45, and 47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *6*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicants election without traverse, of the species of arsenate.

2. Claims 1-52 are pending. Claims 6-11, 13, 19-24, 26, 41-44, 46 and 48-52, drawn to non-elected species, are withdrawn from consideration. Claims 1-5, 12, 14-18, 25, 27-40, 45 and 47 are examined on the merits.

Claim Objections

3. Claim 36-38 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 36 embodies the method of claim 18 wherein the host has cancer. However, claim 18 is drawn to a method of treating cancer, therefore claim 36 is redundant.

4. Claim 39 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 31. Likewise, claim 47 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 40. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 31 is drawn to the method of claim 18 wherein the first and second

compositions are contained within a pharmaceutically acceptable composition. Claim 39 is drawn to the method of claim 18 wherein the first and second compositions are combined in a single formulation. Claim 40 is drawn to a composition comprising 2-methoxyestradiol and a second compound which increases intracellular superoxide. Claim 47 embodies the composition of claim 40 wherein said composition is a pharmaceutically acceptable composition.

Without a recitation of a specific limitation of "pharmaceutically acceptable" the methods of claim 31 are not patentably distinct from the methods of claim 39 and the products of claim 47 are not patentably distinct from the products of claim 45.

Claim Rejections - 35 USC § 112

5.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 28-35 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations of "said first composition" and "said second composition" lack antecedent basis in claim 18.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) in view of Mukhopadhyay et al (U.S. 5,958,892, reference A14 of the IDS filed October 16, 2001).

Claim 1 is drawn to a method of killing a cell comprising contacting a cell with a first composition comprising an agent that increases intracellular superoxide, and contacting said cell with a second composition comprising 2-methoxyestradiol. Claim 2 embodies the method of claim 1 wherein said cell is a cancer cell. Claim 3 specifies that said cancer cell be derived from a solid tumor. Claim 4 embodies the method of claim 1 wherein said cell is a human cell. Claim 12

embodies the method of claim 1, wherein the agent that increases intracellular superoxide comprises an arsenate. Claims 14-16 embody the method of claim 1 wherein the administration of the first composition is concurrent, subsequent, prior to the administration of said second composition, respectively. Claim 17 embodies the method of claim 1 wherein said first and second compositions are combined in a single formulation.

Claim 18 is drawn to a method of treating cancer comprising administering to a host a composition comprising 2-methoxyestradiol and an agent which increases intracellular superoxide. Claim 25 embodies the method of claim 18 wherein the agent that increases intracellular superoxide comprises an arsenate. Claims 28-30 embody the method of claim 18 wherein the administration of the first composition is concurrent, subsequent, prior to the administration of said second composition, respectively. Claim 31 embodies the method of claim 18 wherein said first and second compositions are combined in a pharmaceutically acceptable composition. Claim 32 specifies that the pharmaceutically acceptable composition includes a pharmaceutically acceptable carrier. Claims 33-35 embody the method of claim 31, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, and injection, respectively. Claim 36 embodies the method of claim 18 wherein the host has cancer. Claims 37 and 38 specify a solid tumor and leukemia, respectively. Claim 39 embodies the method of claim 18 wherein the first and second compositions are combined in a single formulation.

Claim 40 is drawn to a composition comprising 2-methoxyestradiol and a second compound which increases intracellular superoxide. Claim 45 specifies that the agent that

increases intracellular superoxide comprises an arsenate. Claim 47 embodies the composition of claim 40 wherein said composition is a pharmaceutically acceptable composition.

Uckun et al teach a method for treating leukemia or breast cancer comprising the administration of an arsenate to a subject (claims 11-13) and a method for inducing cytotoxicity in a cell (claims 14-17) comprising administering an composition comprising arsenate. Uckun et al teach pharmaceutical composition comprising arsenates and pharmaceutically acceptable carriers and methods of treatment comprising oral, parenteral and injection administration of said arsenates (column 5, line 51 to column 6, line 41). Uckun et al teach that the compositions and methods are effective at inducing apoptosis in cancer cells and can be administered to a human patient (column 5, lines 52-54). Uckun et al do not teach the combination of the arsenate compounds with 2-methoxyestradiol, or increasing intracellular superoxide by the administration of the arsenate compounds.

Mukhopadhyay et al teach a method for the treatment of cancer comprising the induction of apoptosis in cancer cells by administration of 2-methoxyestradiol. Mukhopadhyay et al teach the combination of treatment with 2-methoxyestradiol with at least one chemotherapeutic agent (column 20, lines 54-67). Mukhopadhyay et al teach that the cancer cell is derived from a solid tumor (claims 1-7). Mukhopadhyay et al teach the a single composition or pharmaceutical formulation that comprises both agents, or the administration of both agents, in distinct compositions at the same time. Mukhopadhyay et al teach that the treatment with 2-methoxyestradiol may precede or follow the treatment with the chemotherapeutic agent (column

21, lines 5-39), thus fulfilling the specific embodiments of claims 14-17 and 28-32 and 39. Mukhopadhyay et al do not specifically teach the combination of 2-methoxyestradiol with an arsenate agent.

The instant situation is amenable to the type of analysis set forth *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose In order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been taught individually In the prior art. Applying the same logic to the instant method and composition claims, given the teaching of the prior art of methods of inducing apoptosis In solid tumor by the administration of 2-methoxyestradiol as taught by Mukhopadhyay et al and the method of inducing apoptosis In a solid tumor by the administration of the arsenate compounds of Uckun et al, it would have been obvious to combine both 2-methoxyestradiol and arsenates for the treatment of solid tumors because the idea of doing so would have logically followed from their having been individually taught In the prior art to be useful as agents for treating tumors by the induction of apoptosis In tumor cells. Furthermore, It would have been *prima facia* obvious to one of ordinary skill In the art at the time the claimed invention was made to combine administration of arsenate with administration of 2-methoxyestradiol.. One of ordinary skill In the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mukhopadhyay et al on the combination of 2-methoxy estradiol with other chemotherapeutic agents and the teachings of

Uckun et al on arsenates as chemotherapeutic agents. Although neither reference teaches that arsenate compounds increase intracellular superoxide levels, there would be motivation to combine both 2-methoxyestradiol and the arsenate compounds taught by Uckun et al for the reasons set forth above. Therefore, the increase In intracellular superoxide levels, although not relied upon to render obvious the combination, would be inherent In combined method.

9. Claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) In view of Mukhopadhyay et al (U.S. 5,958,892) and the abstract of Barchowsky et al (Toxicology and Applied Pharmacology, !999, Vol. 159, pp. 65-75). The embodiments of the claims are set forth above.

Uckun et al teach a method for treating leukemia or breast cancer comprising the administration of an arsenate to a subject (claims 11-13) and a method for inducing cytotoxicity In a cell (claims 14-17) comprising administering an composition comprising arsenate. Uckun et al teach pharmaceutical composition comprising arsenates and pharmaceutically acceptable carriers and methods of treatment comprising oral, parenteral and injection administration of said arsénates (column 5, line 51 to column 6, line 41). Uckun et al teach that the compositions and methods are effective at inducing apoptosis In cancer cells and can be administered to a human patient (column 5, lines 52-54). Uckun et al do not teach the combination of the arsenate compounds with 2-methoxyestradiol.

Mukhopadhyay et al teach a method for the treatment of cancer comprising the induction of apoptosis In cancer cells by administration of 2-methoxyestradiol. Mukhopadhyay et al teach the combination of treatment with 2-methoxyestradiol with hydrogen peroxide (column 20, lines 54-67 and column 21, lines 58-61). Mukhopadhyay et al teach that the cancer cell is derived from a solid tumor (claims 1-7). Mukhopadhyay et al teach the a single composition or pharmaceutical formulation that comprises both agents, or the administration of both agents, In distinct compositions at the same time. Mukhopadhyay et al teach that the treatment with 2-methoxyestradiol may precede or follow the treatment with the chemotherapeutic agent (column 21, lines 5-39), thus fulfilling the specific embodiments of claims 14-17 and 28-32 and 39. Mukhopadhyay et al do not specifically teach the combination of 2-methoxyestradiol with an arsenate agent.

The abstract of Barchowsky et al teaches that vascular endothelial cells exhibited increased superoxide and hydrogen peroxide accumulation when exposed to low levels of arsenic.

It would have been *prima facia* obvious to one of ordinary skill In the art at the time the claimed invention was made to administer 2 methoxyestradiol and arsenate In a method of treating cancer In a host and a method of killing a cell. One of ordinary skill In the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mukhopadhyay et al on the efficacy of combining treatment with 2-methoxyestradiol with hydrogen peroxide, and the teachings of the abstract of Barchowsky et al regarding increased superoxide and hydrogen peroxide accumulation In vascular endothelial cells exposed to arsenic.

Although neither Mukhopadhyay et al nor Uckun et al teach the necessity of increasing intracellular superoxide levels, there would be motivation to combine both 2-methoxyestradiol and the arsenate compounds taught by Uckun et al because Mukhopadhyay et al teaches the combination with hydrogen peroxide and Barchowsky et al teaches that arsenic exposure causes an accumulation of hydrogen peroxide. Therefore, the increase In intracellular superoxide levels, although not relied upon to render obvious the combination, would be inherent In combined method as evidenced by Barchowsky et al.

10. Claims 1-5, 12, 14-18, 15, 27-40, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) In view of Mukhopadhyay et al (U.S. 5,958,892) and the abstract of Barchowsky et al as applied to claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 in section 9 above, and further In view of the abstract of Oldham et al (Proceed Amer Assoc Cancer Res, 2000, Vol. 41, page 766, reference C23 of the IDS filed October 16, 2001). The embodiments of claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 are set forth In section 8, above.

Claim 4 is drawn to the method of claim 2 wherein said cancer cell is a leukemia cell. Claim 38 is drawn to the method of claim 36, wherein said cancer is leukemia.

The combination of Uckun et al and Mukhopadhyay et al and the abstract of Barchowsky et al render obvious claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 for the reasons set forth In section 9 above.

Uckun et al teach a method for treating leukemia or breast cancer comprising the administration of an arsenate to a subject (claims 11-13) and a method for inducing cytotoxicity In a cell (claims 14-17) comprising administering an composition comprising arsenate. Uckun et al teach that the compositions and methods are effective at inducing apoptosis In cancer cells (column 5, lines 52-54).

Mukhopadhyay et al teach a method for the treatment of cancer comprising the induction of apoptosis In cancer cells by administration of 2-methoxyestradiol. Mukhopadhyay et al teach that the cancer cell is derived from a solid tumor (claims 1-7). Mukhopadhyay et al do not teach a method for treating leukemia comprising the administration of 2-estradiol.

The abstract of Oldham et al teaches that 2-methoxy estradiol selectively kills leukemia cells and that this killing is a result of inhibition of superoxide dismutase by 2-methoxyestradiol. The abstract further teaches that superoxide dismutase is a key enzyme responsible for protecting cells from free-radical damage due to superoxide radicals.

It would have been *prima facia* obvious to one of ordinary skill In the art at the time the claimed invention was made to administer 2 methoxyestradiol and arsenate In a method of treating leukemia and a method of killing a leukemia cell. One of ordinary skill In the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mukhopadhyay et al on the efficacy of combining treatment with 2-methoxyestradiol with hydrogen peroxide, and the teachings of the abstract of Barchowsky et al regarding increased superoxide and hydrogen peroxide accumulation In vascular endothelial cells exposed to arsenic,

and the abstract of Oldham et al on the selective killing of leukemia cells taken from patients by 2-methoxyestradiol, wherein the 2-methoxyestradiol inhibited superoxide dismutase. One of skill In the art would be motivated to combine 2-methoxyestradiol and arsenate In order to inhibit superoxide dismutase by 2-methoxyestradiol and then increase the level of superoxide radicals by the administration of arsenates.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

January 13, 2003